REMARKS

The application was filed with claims 1-114. Claims 6-10, 19, and 46-114 have been previously withdrawn from consideration. By this preliminary amendment claims 1, 12-14, 16, 20, 22, and 43 have been amended; claim 11 has been cancelled. Applicants reserve the right to pursue the withdrawn claims in subsequent continuation applications. Upon entry of the amendments, claims 1-5, 12-18 and 20-45 are pending and under examination on the merits.

Claim 1 is amended to add the limitation of originally filed claims 11-14, 16, 20, 22, and 43. No new matter has been added by the amendments.

Claim 11 has been cancelled; the subject matters of claim 11 have been incorporated into claim 1.

Claim 12-14, 16, 20, 22, 43 have been amended to depend from claim 1. No new matter has been added by the amendments.

The Examiner has rejected claims 1-5, 11-18, and 20-45 in the final Office Action dated December 1, 2004. The Applicants have filed Remarks, without claim amendments, in a Response to the final Office Action on May 27, 2005 to present the Applicants' position. The Examiner, via an Advisory Action mailed on June 13, 2005, has found Applicants' Remarks with respect to all rejections unpersuasive and has maintained all rejections of record in the Final Office Action. Applicants file this Request for Continue Examination with claim amendments and remarks to further present their positions to the Examiner.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-5, 11-18, and 20-45 under 35 U.S. C. § 112, first paragraph, as not enabled. The Examiner states:

> while being enabling for the particular compounds having the particular formula herein as FBPase inhibitor in combination with glyburide and other particular agents as insulin secretagogue, employed in composition herein, does not reasonably provide enablement for co-administering any compounds represented by a FBPase inhibitor and an insulin secretagogue recited in the claims herein. (Office Action pp. 2-3)

Applicants have amended the claims in conformity with the Examiner's statements thereby obviating the Examiner's rejection. Accordingly, claim 1 has been amended limiting the compositions to employ FBPase inhibitors having particular formulae cited in claim 11 and the definitions of M cited in claims 12-14, 16, 20, 22, and 43 in the application, and insulin secretagogues selected from glyburide and other particular agents cited in the application. The selected compounds are fully described in the specification by formulae and/or structures and are therefore in full compliance with the written description requirements set out in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (CAFC, 1997) at 1406. Accordingly, Applicants respectfully request the Examiner to withdraw the rejections of claims 1-5, 11-18 and 20-45 under 35 U.S.C. §112, first paragraph.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 11 and 13 as being indefinite because the expression "**M**" in claim 11 renders claims 11 and 13 indefinite. The Examiner alleges that the expression "**M**" is not understood since "**M**" is not defined in the formula I. The Examiner concludes that, therefore, the

scope of the claims is indefinite as to the structural formula encompassed thereby. (Office Action p. 12)

The Applicants have amended the claims to be in full compliance with 35 U.S.C. § 112, Second Paragraph. Claim 1 has been amended to include the limitations of claim 11 and to include the definitions of M in claims 12-14, 16, 20, 22 and 43, thereby obviating the Examiner's rejection. Accordingly, the Applicants respectfully request that the Examiner withdraw the rejections to claims 11 and 13 under 35 U.S.C. § 112, Second Paragraph.

Claim Rejections - 35 U.S.C. § 103

The Examiner has rejected claims 1-5, 11-18, and 20-45 under 103(a) as being unpatentable over Kasibhatla *et al.* (WO 98/39342, WO 98/39343, WO 98/39344, PTO-892) and Melchior *et al.* (*Annals of Pharmacotherapy*, **1996**, *30(2)*:158-64, PTO-892). The Examiner alleges that Kasibhatla *et al.* (WO 98/39342, WO 98/39343, and WO 98/39344) discloses analogs of particular compounds of the present invention, for example having the formula 1 (azaindole) in WO 98/39342, the formula 1 (benzimidazole) in WO 98/39343, and the formula 1 (purine) in WO 98/39344, being FBPase inhibitors at the AMP site, that are useful in a composition and a method of treating diabetes in a mammal. The Examiner further alleges that Melchior *et al.* teaches that a particular insulin secretagogue, sulfonylureas such as glyburide, are well known to be useful in a composition and in the treatment of diabetes in a mammal. The Examiner notes that the prior art does not expressly disclose the employment of the particular FBPase inhibitor of Kasibhatla *et al.* in combination with the particular insulin secretagogues, *e.g.*, sulfonylureas such as glyburide in a composition for the treatment of diabetes. However, the Examiner asserts that it would have been obvious to a person of

ordinary skill in the art at the time the invention was made to employ the particular FBPase inhibitor of Kasibhatla *et al.* in combination with particular insulin secretagogues, sufonylureas such as glyburide, in a composition for the treatment of diabetes. The Examiner reasons that one having ordinary skill in the art at the time the invention was made would have been motivated to make the combination, since both the particular FBPase inhibitor of Kasibhatla *et al.*, and secretagogues, in particular sufonylureas such as glyburide, are known to be useful in a composition and a method of treating diabetes in a mammal based on the prior art; and that one of ordinary skill in the art would have reasonably expected that combining the particular FBPase inhibitor of Kasibhatla *et al.* with particular insulin secretagogue, sufonylureas such as glyburide both known to be useful for the same purpose, i.e., treating diabetes, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same. The Examiner cited *In re Kerkhoven,* 205 USPQ 1069, CCPA 1980 which holds that it is prima facie obvious in certain situations to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

The Applicants have carefully analyzed Examiner's reasonings, but respectfully traverse this rejection. Applicants submit that the Examiner has not established prima facie obviousness. To establish prima facie obviousness, first there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success in making the combination. Finally, the prior art reference (or references

when combined) must teach or suggest all the claim limitations. MPEP § 2143. Because the cited references did not teach or suggest that the FBPase inhibitors may be combined with other active ingredients for the treatment of diabetes, there is no teaching or motivation to combine. In addition, even if one of ordinary skill found suggestions to combine, there is no reasonable expectation of success for the combination.

Applicants submit that Melchior *et al.* in view of Kasibhatla *et al.* do not teach or suggest the combination of the invention; Melchior *et al.* actually warn against some combinations of antidiabetic drugs. Melchior *et al.* reviews the comparative efficacy of metformin, sulfonylureas, and insulin in the treatment of patients with type II diabetes. Melchior *et al.* discloses that patients who do not achieve adequate glycemic control at appropriate daily doses of sulfonylureas, such as glyburide, probably would be better served by adding metformin rather than further escalating the sulfonylurea dosage. See Melchior *et al.*, p. 162. Metformin is a biguanide ($((CH_2)_2NC(NH)NHC(NH)NH_2$) and is most accurately classified as an antihyperglycemic agent. Metformin decreases plasma glucose concentrations and is ineffective in the absence of insulin. *See,* Melchior et.al., p. 158-159. The mechanism of action of this class of compounds is still unclear, but in recent years, it was established that the glucose lowering effect of Metformin is largely due to its inhibition of hepatic glucose output. *See,* Specification, p. 2, ll. 27-29. Melchior *et al.* speculate the decreased hepatic glucose output may be the result of increased glucose oxidation. *See,* Melchior *et al.* p. 159. Nowhere does Melchior *et al.* suggest that metformin can be used in combination with any other antidiabetic drugs. The reference openly questions whether metformin has a place in combination with insulin therapy in the treatment of either type I or type II diabetes. *See,* Melchior *et al.* p. 162, right column. It should therefore be understood that a successful combination of

metformin with sulfonylurea does not automatically imply that other combinations of antidiabetic drugs would be at all successful.

Kasibhatla *et al.* (WO 98/39342, WO 98/39343, and WO 98/39344) discloses FBPase inhibitors having the formula 1 (azaindole) in WO 98/39342, the formula 1 (benzimidazole) in WO 98/39343, and the formula 1 (purine) in WO 98/39344, and the use of these compounds in the treatment of diabetes, and other diseases where the inhibition of gluconeogenesis, control of blood glucose levels, reduction in glycogen stores, or reduction in insulin levels is beneficial. *See,* WO 98/39342, p. 1, ll. 5-10, p. 5, ll. 5-14; WO 98/39343, p. 1, ll. 5-10; WO 98/39344, p. 1, ll. 5-10. The compounds of Kasibhatla *et al.* and of the current invention are generally phosphate or phosphonate derivatives. *See,* specification, pages 26-28. These compounds reduce serum glucose concentration by the inhibition of fructose-1,6-bisphosphatase, one of the enzymes that catalyze gluconeogenesis. Preferred FBPase inhibitors are compounds that inhibit enzyme activity as determined by conducting *in vitro* inhibition studies (Examples A and B). Applicants have carefully reviewed Kasibhatla *et al.* (WO 98/39342, WO 98/39343, and WO 98/39344) and were unable to locate the teachings and suggestions that the compounds can be used with any other active ingredients in a pharmaceutical composition. If Applicants' characterization of the teaching of Kasibhatla *et al.* (WO 98/39342, WO 98/39343, and WO 98/39344) is incorrect, the Applicants would appreciate that the Examiner specifically cite to the location of such teachings.

As the Examiner admits, the prior art references cited together do not teach the composition of the invention. The current invention is directed toward compositions containing insulin secretagogues and FBPase inhibitors. Melchior *et al.* teaches only the combination of sulfonylurea with metformin for glycemic control and further implies that not all antidiabetic drugs can be

combined successfully. Kasibhatla *et al.* is silent on whether the FBPase inhibitors can be combined with other drugs to improve the glycemic control effect. The Applicants respectfully submit that there is no suggestion or teaching in Melchior *et al.* or in Kasibhatla *et al.*, alone or in combination, to motivate one skilled in the art to combine, the FBPase inhibitors of Kasibhatla *et al.* with the sulfonylurea of Melchior *et al.* to form the pharmaceutical composition of the present invention.

Further, although improved glycemic control is a reported consequence of treatment with either insulin secretagogues or FBPase inhibitors, those skilled in the art would not have any reasonable expectation the combination would function successfully. The Examiner has recognized that the pharmaceutical art is highly unpredictable due to the complexity of the biological system. One successful combination of metformin and sulfonylurea is not indicative that the combination of FBPase inhibitors and sulfonylurea would be equally successful. In particularly the Applicant notes that metformin is distinct in structure, in its site of action and biochemical mechanism from the FBPase inhibitors.

The Examiner cites to *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) to assert a prima facie case of obviousness. The Applicants respectfully submit that it is inappropriate to apply the holding of *In re Kerkhoven* to the instant case. The *Kerkhoven* Court, citing *In re Susi,* 169 USPQ, 423, 426 (CCPA 1971) and *In re Crockett and Hulme,* 126 USPQ 186, 188 (CCPA 1960), held that "it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for very same purpose; [the] idea of combining them flows logically from their having been individually taught in prior art." *Id.* at 1972. In *In re Kerkhoven*, the Court ruled that claims to a process of preparing a spray-dried detergent by mixing together two conventionally spray-dried detergents were prima facie obvious.

In *In re Crockett*, the Court held that claims directed to a method and composition for treating cast iron using a mixture comprising calcium carbide and magnesium oxide was unpatentable over prior art which disclosed that the aforementioned components individually promote the formation of a desired nodular structure in cast iron. In *In re Susi*, the Court held that claims to additives for stabilizing plastics against oxidative effects were unpatentable over prior art which discloses generic claims of the compounds that nearly cover the additives of the invention. Each of the above cases were decided based on subject matters of the prior art and the claimed invention being closely related, if not the same, which led the court to expect that, in combination, the ingredients would produce the same effect that they produced individually and would supplement or at least replace each other.

In the instant case, the subject matter of the invention is neither closely related to nor equivalent to the subject matters in the cited references. The two substances that are combined by the present invention do not perform the same function: they have different biochemical effects. And the substance in the Melchior *et al.* combination, metformin, that is replaced by the FBPase inhibitor of Kasibhatla *et al.* does not have the same biochemical effect as the metformin it replaces.

Melchior *et al.* discloses a combination of metformin and sulfonylurea. Kasibhatla *et al.* discloses FBPase inhibitors. The current invention is directed toward compositions containing insulin secretagogues, exemplified by sulfonylurea, and FBPase inhibitors. To establish a prima facie case of obviousness under the guidance of *In re Kerkhoven*, the FBPase inhibitors of Kasibhatla *et al.* need to be equivalent to the metformin of Melchior *et al.* The FBPase inhibitors of the present inventions are phosphate or phosphonate derivatives, therefore they are structurally distinct from metformin which is a biguanide. More importantly, the sites of action and modes of

operation of the FBPase inhibitor compounds are substantially different from those of metformin: the two are not shown to be equivalent or interchangeable merely by the fact that both are useful to treat some aspect of diabetes. Applicants respectfully submit that the FBPase inhibitors are neither closely related nor equivalent to metformin, and the combination of insulin secretagogues with a FBPase inhibitor forming the pharmaceutical composition of the invention is at most obvious to try.

The Applicants further submit that the combination of the present invention produces unexpected benefits which would not have been foreseeable. Such unexpected results are recognized as evidence that the combination is nonobvious.

Although improved glycemic control is a reported consequence of treatment with an insulin secretagogue or FBPase inhibitor, prior to this study there was no evidence that the inhibition of FBPase could extend the pharmaceutical effectiveness of an insulin secretagogue in type 2 diabetes well into the advanced stages of the disease. Insulin secretagogues are primarily effective in early stage of NIDDM during which all, or some, pancreatic insulin secretory capacity is preserved. It has been shown that insulin secretagogues have a high failure rate in older, insulin-resistant animals with poor pancreatic insulin secretory function such as the ZDF rats used in the combination study. *See,* Specification, p. 206. ll. 24-31. Treatment with an insulin secretagogue alone becomes less effective as pancreatic function declines leading to secondary failure. Surprisingly, the combination treatment of an insulin secretagogue and an FBPase inhibitor not only provided improved glycemic control in early stage diabetes (Example X), but also resulted in significantly better glycemic control over the entire course of study thus, allowing the insulin secretagogue to remain effective over longer period of time (Example Y).

The Examiner asserts that their common utility for treating diabetes is sufficient basis for combining an FBPase inhibitor with a secretagogue. However, even if there was sufficient suggestion to try the combination, it was not sufficient basis to expect the combination to successfully work. In this study (Example X) both the insulin secretagogue and the FBPase inhibitor were administered at their maximally efficacious dose for controlling blood glucose level: increasing the dosage of either drug alone above this level used would not provide a significant added benefit. The glycemic control that resulted from the combination of this invention was greater (approximately 20%) than the additive effective of administration of either agent alone (*See,* p. 316, ll. 32-34, Figure 1, p. 317). This is unexpected. At the maximally efficacious dose, increasing the amount of drug would give you less than a linear dose response. The dose response curve flattens out, such that if the dose is doubled, the effect does not double. Thus, it is unexpected that a second drug, also at its maximally efficacious dose, would lead to an at least additive effect. Even if a person of ordinary skill in the art might have expected that the combination of insulin secretagogues or FBPase inhibitors would result in glycemic control, they would not have known that the combination of this invention would result in significantly greater glycemic control than that obtained by administration of either agent alone. Therefore, the significantly improved glycemic control obtained with the combination of insulin secretagogues or FBPase inhibitors was surprising and unexpected.

Additionally, both the secretagogues and the FBPase inhibitors are known to cause certain side effects; and it could not have been known or reasonably expected that combining the two could be done without adverse consequences. As the Applicants have demonstrated, the side effects of the individual active ingredients were moderated by the combination. For instance, blood lactate

elevations were suppressed by the combination of the invention. (Example X, p. 315-317). FBPase inhibitor therapy is characterized by the elevation of blood lactate, whereas insulin secretagogue therapy is not known to modulate blood lactate levels. It is therefore totally surprising that the elevation of blood lactate levels did not occur in the combination therapy. Specification, p. 208, ll. 4-18, Example X, p. 316. The elevation of blood lactate is undesirable in man as it can lead to severe metabolic disturbances. Lactic acidosis is a rare, potentially fatal complication resulting from the treatment of NIDDM patients with metformin which has resulted in its contraindication in chronic hypoxic conditions including cardiovascular, renal, pulmonary, and hepatic disease as well as advancing age *See,* Howlett, H.C. and Baily, C.J. *Drug Safety* **1999,** *20(6)* 489-503.

Another benefit of the combination therapy is that FBPase inhibitors can attenuate the side effects associated with insulin secretagogue therapy. A key consequence of insulin secretagogue therapy is hyperinsulinemia which results in the undesirable side effects of promoting weight gain, of exacerbating insulin resistance, and of predisposing patients to hypoglycemic episodes. Hyperinsulinemia may also be associated with increased risk of macrovascular disease. Insulin secretagogues can also overstimulate the pancreas and consequently promote beta cell degeneration and thus secondary failure. As illustrated in Examples AA and BB, combination therapy significantly reduced the weight gain observed on insulin monotherapy. Also illustrated in Examples AA and BB is the surprising observation that co-administration of an FBPase inhibitor allowed a significant reduction in the insulin dose, while the same gylcemic control as in the insulin monotherapy group was maintained. This insulin sparing effect is likely to reduce the risk of above described side effects associated with insulin therapy.

In summary, the combination of FBPase inhibitor therapy with insulin secretagogue therapy resulted in several unexpected metabolic effects: (1) better glycemic control over long term treatment, (2) an at least additive effect even when each drug is administered at its maximal effective dose, and (3) an attenuation of side effects associated with FBPase monotherapy, notably blood lactate elevation.

The present invention combines two types of drugs known to have both beneficial and adverse effects. The prior art informs one of ordinary skill that such combinations may accentuate either the beneficial or the adverse effects of such individual drugs. *See,* Melchior *et al.* p. 162, right column. Nothing in the prior art suggests that combining these two types of drugs would reduce adverse effects and maintain or increase beneficial effects. Thus there could be no expectation of success when making the combination of the present invention: that distinguishes this situation from Kerkhoven, which dealt with predictable properties of materials combined together, where each material seems to do substantially the same thing.

The prior art does not teach or suggest combining the two types of diabetes-treating drugs involved in the present invention, namely an FBPase inhibitor and an insulin secretagogue. Even if the prior art would have suggested the combination of an FBPase and an insulin secretagogue, the prior art could not have provided a reasonable expectation of success with the combination, because it provided no way to know if the beneficial effects of the separate treatments would be additive, particularly at each drug's maximally effective dose, and no way to predict that the adverse effects would not be additive or greater. As the application demonstrates, the combination provides not only an addition of the beneficial effects, but it also significantly reduces the adverse effect of FBPase monotherapy.

In view of the above, the Applicants respectfully request that the Examiner withdraw the obviousness rejection.

Double Patenting

The Examiner provisionally rejects claims 1-5, 11-18, and 20-45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over all the claims of copending Application No. 09/470649. The Examiner alleges that although the conflicting claims are not identical, they are not patentably distinct from each other. The Examiner alleges that the claims of the copending application is drawn to COMBINATION OF FBPASE INHIBITORS AND INSULIN SENSITIZERS FOR THE TREATMENT OF DIABETES and that the claims of the instant application are drawn to employ the same FBPase inhibitor in combination with insulin secretagogue, such as sulfonylureas, *e.g.* glyburide in a composition for the treatment of diabetes. The two compositions in the copending Application and the instant Application are seen to substantially overlap; Office Action, p. 17. The Examiner further alleges that the particular insulin secretagogue, sulfonylureas, *e.g.*, glyburide, would be reasonably interpreted as an insulin sensitizer for the treatment of diabetes as claimed in the copending Application. Thus, the two compositions in the copending Application and the instant Application are seen to be obvious to each other. Office Action, p. 18.

The Applicants would like to inform the Examiner that Application No. 09/470649 has been allowed and issued as U.S. Patent No. 6,756,360.

The Applicants respectfully traverse the double patenting rejection. The Applicants respectfully submits that insulin secretagogues and insulin sensitizers are distinctly different types of

agents; they act on different sites and have different modes of operation. The Applicants have provided in the respective applications clear and detailed description for each of these agents and ample examples to illustrate the boundary of the claimed invention. There should be no confusion.

The insulin secretagogues are commonly prescribed oral agents for glycemic control. Insulin secretagogues target defects in insulin secretion by the pancreas, defects which are typically observed in diabetics. The classical insulin secretagogues, the sulfonylureas: glyburide, glimeperide, and glipizide, stimulate insulin release from the pancreas by binding to adenosine triphosphate (ATP)-dependent potassium channels of the pancreatic beta cell. Other insulin secretagogues include glucagon-like peptide (GLP-1), the primary site of action of which is also the beta cell. Agents that prolong the half-life of GLP-1, i.e. the dipeptidyyl peptidase-IV (DPP-IV) inhibitors, are also being evaluated as insulin secretagogues. *See,* Specification, p. 2, ll.16-26.

Insulin sensitizers are a distinct class of oral agents for glycemic control that act by a different mechanism. These compounds enhance insulin-action without directly stimulating insulin secretion. *See,* Specification, p. 2, l. 30 to p. 3, l. 3. The compounds act on the underlying mechanisms of insulin resistance and thereby lower glucose by enhancing insulin action at both peripheral and hepatic sites. Saltiel & Olefsky, *Diabetes,* **1996,** *45:*1661-1669. Applicants respectfully submit that there are no overlaps between insulin sensitizers and insulin secretagogues by their mode of action. Insulin secretagogue acts by stimulating insulin secretion. Insulin sensitizer act to increase the body's sensitivity to insulin...

U.S. Patent 6,756,360 (the '360 patent), which matured from Application No. 09/470649, claims a pharmaceutical composition comprising a pharmaceutically effective amount of an insulin sensitizer agent and a pharmaceutically effective amount of an FBPase inhibitor or prodrugs or salts

thereof. The current application claims a pharmaceutical composition of an insulin secretagogue with an FBPase inhibitor or prodrugs or salts thereof. The '360 patent and the present application share the same FBPase inhibitors, but the distinction between the insulin secretagogues and insulin sensitizers which form part of the claims renders the current application patentably distinct from U.S. Patent 6,756,360. Accordingly, the Applicants respectfully request removal of the double patenting rejection.

CONCLUSION

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

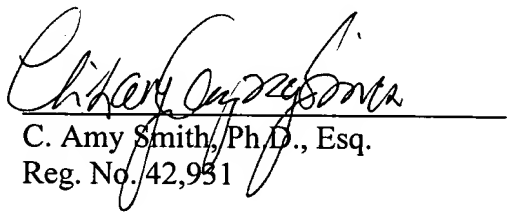
Applicants hereby petition for a 3-month extension of time under 37 CFR § 1.136(a). With the granting of said extension, it is believed that this response is timely filed. The Commissioner is hereby authorized to charge $905.00 to Deposit Account No. 50-2613 for the 3-month extension fee due herein and any other fees that may become due or credit become payable during the pendency of this application.

The Examiner is invited to telephone the undersigned, Applicants' attorney of record, to facilitate advancement of the present application.

If the examiner is not persuaded by the remarks and wishes to maintain her rejection to the claims, the Applicants respectfully ask the Examiner to grant a telephonic interview allowing the Applicants to present their arguments in person. Please contact the undersigned to arrange a time that is convenient to the Examiner.

Respectfully Submitted,

Date: October 26, 2005

By: 

C. Amy Smith, Ph.D., Esq.
Reg. No. 42,931

Paul, Hastings, Janofsky & Walker LLP
P.O. Box 919092
San Diego, CA 92191-9092
Direct Dial: (858)720-2885
Facsimile: (858)720-2555